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CLINICAL PRACTICE GUIDELINES

Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Incidence and epidemiology

Mantle cell lymphoma (MCL) is a relatively uncommon subtype of lymphoid malignancy and represents 5%–7% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000 recently. MCL is more common in males than in women with a 3 : 1 ratio.

Diagnosis and pathology/molecular biology

Diagnosis should be based on a surgical specimen, preferably a lymph node biopsy. Core biopsies should only be carried out in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk), keeping in mind the heterogeneity of MCL. In the rare cases with leukaemic manifestation only, a bone marrow (BM) biopsy may be sufficient if additional diagnostic measures are applied, immunophenotype (CD5+, CD19/20+), detection of t(11;14)(q13;q32) and overexpression of cyclin D1. Fine needle aspirations are inappropriate for a reliable evaluation of additional risk factors (cytology, cell proliferation).

The histological report should give the diagnosis according to the World Health Organization (WHO) classification and Ki-67 as the most established histomorphological risk factor [I, A] [1]. Most tumours have a classic morphology of small-medium sized cells with irregular nuclei. However, the malignant lymphocytes may present with a spectrum of morphological variants, including small round (resembling chronic lymphocytic leukaemia), marginal zone-like, pleomorphic and blastoid cells. In the updated WHO classification, a leukaemic non-nodal subtype has been characterised based on the clinical presentation usually with a more indolent clinical course [1]. As only the minority of these cases is correctly diagnosed based on classical histology only, review by an expert haematopathologist is advised. In particular, additional immunohistochemistry for detection of cyclin D1 overexpression is mandatory.

In the rare cyclin D1-negative cases, detection of SOX11 may help to establish the diagnosis [2].

If possible, additional biopsy material should be stored freshly frozen to allow additional molecular analyses (currently still investigational).

Staging and risk assessment

Since treatment may differ depending on the stage of the disease, initial staging should be thorough, particularly in the rare cases with non-bulky stages I and II (Table 1). Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a BM aspirate and biopsy (Table 2). Positron emission tomography (PET)-CT scan is especially recommended in the rare limited stages I/II, before localised radiotherapy (RT) [IV, C]. Gastrointestinal endoscopy is also recommended in these rare cases to detect asymptomatic involvement but otherwise only in symptomatic patients. Of note, when

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Table 1. Lugano classification [4]

Stage	Area of involvement
I (I_E)	One lymph node region or extranodal site (I_E)
II (II_E)	Two or more lymph node regions or localised extranodal sites (II_E) on the same side of the diaphragm
III	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm
IV	Diffuse or disseminated extralymphatic organ involvement

Table 2. Diagnostic work-up

History	B symptoms
Physical examination	Waldeyer's ring, peripheral lymph nodes, liver, spleen
Laboratory work-up	Blood and differential count In leukaemic cases: FACS (CD5/CD19/20+) FISH for *t(11;14)* recommended LDH, uric acid, liver and renal function Electrophoresis (optional: immune fixation)
Serology	Hepatitis B, C and HIV serology
Imaging	Abdominal ultrasound CT neck, chest, abdomen, pelvis or PET-CT MRI only in selected locations (CNS)
Bone marrow	Histology (cyclin D1 immunohistochemistry) Cytology Recommended: FACS, FISH for *t(11;14)* Optional: PCR for IGH gene rearrangement
Toxicity	Electrocardiogram, cardiac ultrasound (before anthracyclines, ASCT) Pulmonary function (before ASCT) Creatinine clearance Optional: reproductive counselling in young patients

ASCT, autologous stem cell transplantation; CNS, central nervous system; CT, computed tomography; FACS, fluorescence-activated cell sorting; FISH, fluorescent *in situ* hybridisation; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, positron emission tomography.

Table 3. MIPI and MIPI-c risk stratification [6, 7]

Points	Age (years)	ECOG	LDH (ULN)	WBC (10^9/L)
0	< 50	0–1	< 0.67	< 6700
1	50–59	–	0.67–0.99	6700–9999
2	60–69	2–4	1.00–1.49	10 000–14 999
3	≥ 70	–	≥ 1.50	≥ 15 000

MIPI risk group (weight in MIPI-c)	Ki-67 index (weight in MIPI-c)	MIPI-c risk group (sum of weights)
Low (0)	< 30% (0)	Low (0)
Low (0)	≥ 30% (1)	Low-intermediate (1)
Intermediate (1)	< 30% (0)	Low-intermediate (1)
Intermediate (1)	≥ 30% (1)	High-intermediate (2)
High (2)	< 30% (0)	High-intermediate (2)
High (2)	≥ 30% (1)	High (3)

For each prognostic factor, 0–3 points were given to each patient and points were summed up to a maximum of 11. Patients with 0–3 points in summary were classified as low-risk, patients with 4 to 5 points as intermediate-risk, and patients with 6–11 points as high-risk. ECOG performance status was weighted with 2 points if patients were unable to work or bedridden (ECOG 2–4). LDH was weighted according to the ratio to the ULN. Thus, for an ULN of 240 U/L, the limits were 180, 240 and 360 U/L for low-, intermediate- and high-risk groups, respectively.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIPI, mantle cell lymphoma international prognostic index; MIPI-c, combined MIPI; ULN, upper limit of normal range; WBC, white blood count.

analysed, the majority of MCL patients will have gastrointestinal involvement.

Central nervous system (CNS) involvement is rare in asymptomatic patients at diagnosis, but a lumbar puncture may be considered in high-risk cases [at least two of the following risk factors: blastoid variant, elevated lactate dehydrogenase (LDH), impaired performance status or neurological symptoms] [III, C] [3].

A full blood count, blood chemistry including LDH and uric acid, as well as screening tests for human immunodeficiency virus (HIV) and hepatitis B and C, are required. Staging is carried out according to the Lugano classification system (Table 1), with mention of bulky disease > 5 cm when appropriate [4].

The evaluation of the cell proliferation antigen Ki-67 is the most applicable method to evaluate cell proliferation, and is considered the most established biological risk factor in MCL. As the reproducibility of quantitative scores among pathologists may vary, a standardised method has been suggested [5].

For prognostic purposes, a combined MCL International Prognostic Index (MIPI-c) (Table 3; web-based calculator: www.european-mcl.net/de/clinical_mipi.php) has been established [I, A] [6, 7].

Leukaemic non-nodal subtype of MCL

Most patients with MCL follow an aggressive clinical course. However, a subset of patients may exhibit a more indolent evolution. Most of these cases are commonly characterised by a leukaemic non-nodal presentation with BM involvement only and splenomegaly [1, 8]. SOX11 negativity may help to identify these cases. In addition, conventional MCL (SOX11-positive) with low Ki-67 (≤ 10%) tend to have a more indolent course. However, additional *TP53* mutations may cause an aggressive clinical evolution (Figure 1) [9].

Unfortunately, there are no markers that definitely predict indolent behaviour, but a short course of 'watch and wait' period under close observation seems to be appropriate in suspected indolent cases with low tumour burden [III, B] [10].

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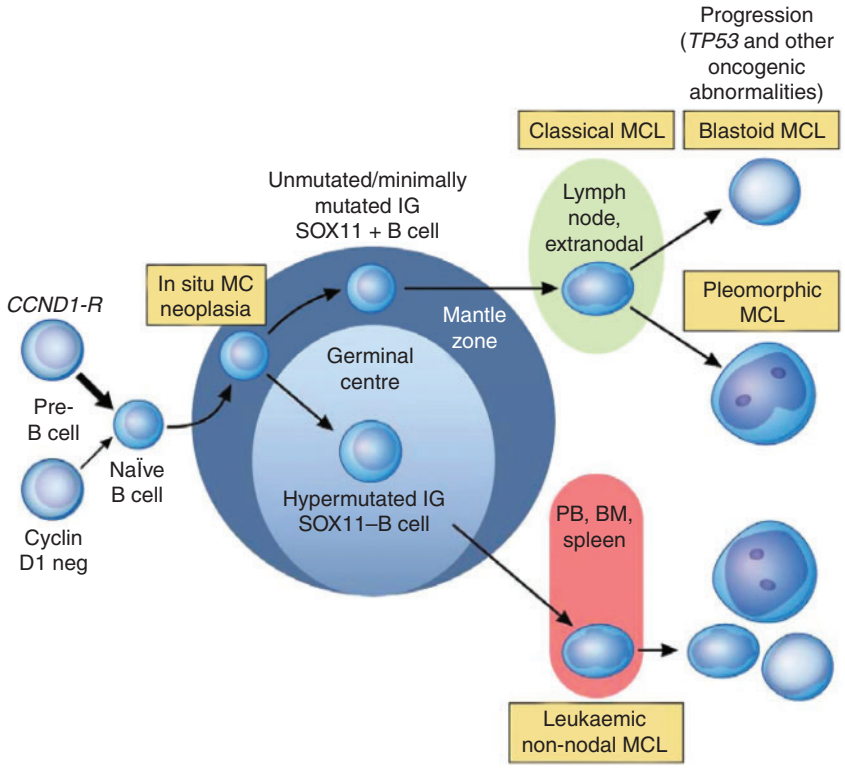

Figure 1. Molecular pathogenesis of MCL.
BM, bone marrow; IG, immunoglobulin; MC, mantle cell; MCL, mantle cell lymphoma; neg, negative; PB, peripheral blood.
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If treatment is required, recommendations for classical MCL apply.

Treatment

First-line

Stages I–II. In the small proportion of patients with limited non-bulky stages I–II, RT (involved field, 30–36 Gy) has been suggested to achieve long-term remissions [11]. In contrast, in a randomised study, all patients with early-stage MCL relapsed within 1 year [12]. Thus, a shortened conventional chemotherapy (ChT) induction followed by consolidation RT (similar to diffuse large cell lymphoma) may be the most appropriate treatment in these cases [IV, B].

In stage I–II patients with large tumour burden or adverse prognostic features, systemic therapy as indicated for advanced stages should be applied; consolidation RT may be considered depending on tumour location and expected side-effects [IV, B].

Stages III–IV

Induction: In all symptomatic patients and generally in cases with high tumour burden, therapy should be initiated at diagnosis [I, A]. The current therapeutic approach is based on clinical risk factors, symptoms and patient characteristics (Figure 2).

Elderly patients: Based on a median age of 65 years at first diagnosis, the majority of patients do not qualify for dose-intensified regimens. Three prospective first-line trials, a salvage trial and a systematic meta-analysis support an improved overall response, progression-free survival (PFS) and overall survival (OS) if rituximab was added to ChT (Table 4) [I, A] [13].

Rituximab in combination with ChT such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine should be used [I, B] [14–16]. Recently, a combination with bortezomib achieved almost doubled median PFS but resulted in significant thrombocytopaenia [17]. Rituximab in combination with cyclophosphamide, vincristine and prednisone (R-CVP) resulted in inferior response rates and PFS [18]. Purine analogue-based schemes, rituximab with fludarabine and cyclophosphamide (R-FC) or with fludarabine and mitoxantrone (R-FM), are also discouraged due to early failures and long-lasting myelosuppression [I, D] [15]. The addition of high-dose cytarabine (HD-AraC) to CHOP is currently being tested in elderly patients. Recently, rituximab, bendamustine and cytarabine (R-BAC) has been explored also in first-line therapy [19].

In frail patients, a less intense immunochemotherapy, chlorambucil or vincristine, doxorubicin, oral dexamethasone and chlorambucil (VADC) or prednisone, etoposide, procarbazine and cyclophosphamide (PEP-C) may be considered, aiming primarily at palliation [II, B]. However, targeted therapy exhibiting a low toxicity profile might be used in this population [20].

Antibody monotherapy [rituximab, radioimmunotherapy (RIT)] achieves only moderate response rates and is therefore not recommended [III, B] [21].

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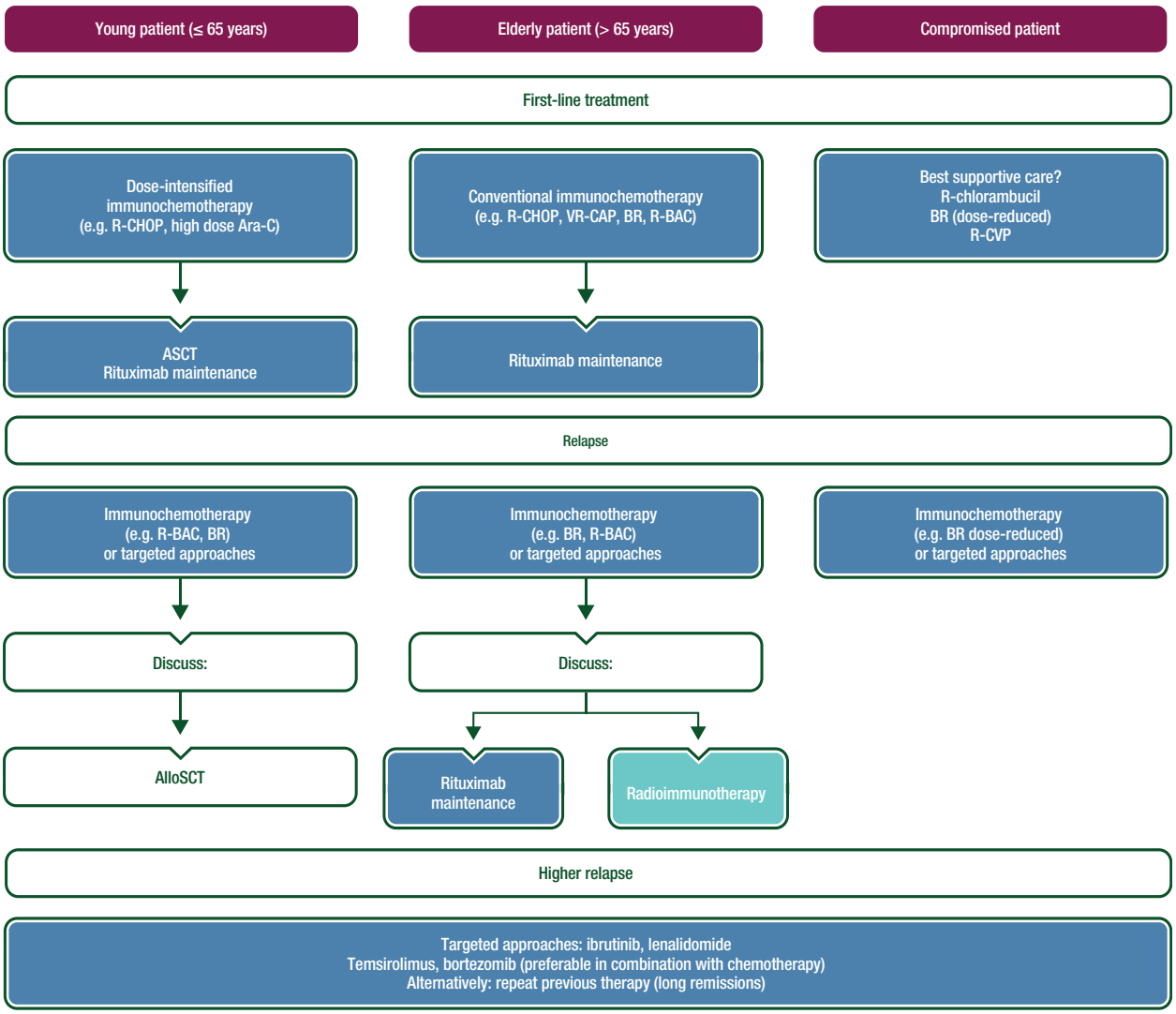
Young patient (≤ 65 years)
Elderly patient (> 65 years)
Compromised patient
First-line treatment
Dose-intensified immunochemotherapy (e.g. R-CHOP, high dose Ara-C)
Conventional immunochemotherapy (e.g. R-CHOP, VR-CAP, BR, R-BAC)
Best supportive care? R-chlorambucil BR (dose-reduced) R-CVP
ASCT Rituximab maintenance
Rituximab maintenance
Relapse
Immunochemotherapy (e.g. R-BAC, BR) or targeted approaches
Immunochemotherapy (e.g. BR, R-BAC) or targeted approaches
Immunochemotherapy (e.g. BR dose-reduced) or targeted approaches
Discuss:
Discuss:
AlloSCT
Rituximab maintenance
Radioimmunotherapy
Higher relapse
Targeted approaches: ibrutinib, lenalidomide
Temsirolimus, bortezomib (preferable in combination with chemotherapy)
Alternatively: repeat previous therapy (long remissions)

Figure 2. Therapeutic recommendations.
AlloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BAC, bendamustine and cytarabine; BR, bendamustine and rituximab; Ara-C, cytarabine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CVP, cyclophosphamide, vincristine and prednisone; R, rituximab; VR-CAP, rituximab, cyclophosphamide, doxorubicin and prednisone with bortezomib.

In patients with positive hepatitis B serology, prophylactic antiviral medication and/or virus load monitoring is strongly recommended [I, A] [22].

Consolidation/maintenance. Rituximab maintenance significantly improves PFS and OS after rituximab and CHOP (R-CHOP) [I, A] and PFS in a systematic meta-analysis [15, 23].

RIT consolidation also prolongs PFS after ChT, but its benefit seems to be inferior in comparison to rituximab maintenance [II, B] [24].

Younger patients: Although no curative treatment is available for MCL so far, an intensive approach, e.g. by autologous stem cell transplantation (ASCT), has been demonstrated to induce higher response and survival rates in fit patients, independently of the addition of rituximab [I, B] (Table 5) [25–27].

In addition, a randomised trial confirmed that a cytarabine-containing induction achieves a significantly improved median time to treatment failure ($P = 0.038$) [I, B] [28]. In contrast, an induction-based on HD-AraC alone achieves only insufficient response rates [III, D] [29].

In a retrospective study comparison of the Nordic, HOVON and MCL Younger protocols, total body irradiation (TBI) before ASCT was confirmed to be beneficial only in partial response (PR) patients [II, B] [30]. In contrast, the benefit of RIT has not been demonstrated in inter-study comparisons.

An upfront dose-intensified approach (R-hyper-CVAD, rituximab in combination with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate/cytarabine cycles) also achieved very high response and survival rates in phase II studies, but its feasibility is hampered by a significant therapy-associated

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Table 4. Conventional first-line immunochemotherapy in MCL (phase III studies)

Author	Study features	Assessable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	2-Year OS
Lenz et al. [14]	Phase III, randomised	112	CHOP versus R-CHOP	75 (7) versus 94 (34)	21 versus 14 (TTF)	76% versus 76%
Herold et al. [54]	Phase III, randomised	90	MCP versus R-MCP	63 (15) versus 71 (32)	18 versus 20	52% versus 55% (4-year OS)
Kluin-Nelemans et al. [15]	Phase III, randomised	485	R-CHOP versus R-FC	86 (34) versus 78 (40)	58% versus 29% (4-year DOR)	62% versus 47% (4-year OS)
			R versus IFNα			79% versus 67% (4-year OS)
Rummel et al. [16]	Phase III, randomised	514 (94 MCL)	R-CHOP versus BR	91 (30) versus 93 (40)	21 versus 35	No differences
Robak et al. [17]	Phase III, randomised	487	R-CHOP versus VR-CAP	89 (42) versus 92 (53)	16 versus 31	54% versus 64% (4 years)

BR, bendamustine and rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; DOR, duration of response; FC, fludarabine and cyclophosphamide; IFNα, interferon alpha; MCL, mantle cell lymphoma; MCP, melphalan, chlorambucil and prednisone; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; TTF, time to failure; VR-CAP, bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone.

toxicity [II, C] [31–33] and low success rate of stem cell mobilisation.

Rituximab maintenance following a rituximab with dexamethasone, cytarabine and cisplatin (R-DHAP)-based induction and ASCT improves PFS and OS and represents the current standard of care [I, A] [27].

So far, there are no data to support the application of allogeneic stem cell transplantation (alloSCT) as part of front-line treatment [II, D] [34].

Relapsed disease

A repeated biopsy is recommended to identify important prognostic features of MCL.

Selection of salvage treatment depends on efficacy of prior regimens. In early relapses (< 12–24 months), a non-cross-resistant scheme should be preferred [bendamustine or HD-AraC-containing regimens, e.g. rituximab, bendamustine and cytarabine (R-BAC)] after CHOP or vice versa [19]. Rituximab should be added if the previous antibody-containing scheme achieved > 6 months duration of remission [IV, B].

In cases of early relapses or in refractory cases, newer targeted approaches should be strongly considered (Figure 2; Table 6). Among the registered compounds, ibrutinib achieves the highest response rates and, in some cases, long-term remissions [35–37], but early relapses display very aggressive features. When there are contraindications to ibrutinib therapy, particularly a high risk of bleeding, lenalidomide (preferable in combination with rituximab) may also achieve ongoing remissions in some cases [38–41]. Temsirolimus and bortezomib have been shown to be effective but should preferably be applied in combination with ChT based on phase II/III studies [17, 42–45].

Rituximab maintenance has a favourable safety profile and prolongs PFS and OS in relapsed disease [I, A] [46]. However, second-line maintenance approaches have not been investigated in patients relapsing after front-line maintenance [IV, D].

RIT consolidation seems to result in extended remission durations [47, 48] especially in elderly patients with comorbidities not eligible for dose intensification [IV, B].

High-dose ChT with ASCT may be considered in patients relapsed after conventional first-line therapy. However, the benefit seems to be marginal in this setting [49], and there is no role for a second autograft at relapse.

In younger patients, alloSCT is potentially curative and has achieved long-term remissions even in patients following early relapse and with refractory disease [III, B]. Based on the advanced age of most patients, dose-reduced conditioning is appropriate [IV, B] [50]. Haploidentical BM transplantation achieves high response rates but is still experimental in MCL.

Response evaluation

PET-CT according to the Lugano classification for response evaluation is optional [4].

Radiological tests should be carried out mid- and post-completion of ChT. Patients who achieve less than a PR should be considered for early salvage regimens. Patients achieving a PR may convert to a complete response after post-induction treatment.

The independent prognostic role of minimal residual disease (MRD) applying patient-specific primers has been confirmed in numerous studies [51, 52]. However, because of the current

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Table 5. Dose-intensified first-line therapy in MCL (phase II/III trials)

	Study features	Assessable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (years)	Median OS (years)	Dropout rate	TRM	Secondary tumour rate
ASCT-based regimens									
Dreyling et al. [25, 26]	Phase III, randomised	122	CHOP + TBI + ASCT versus CHOP + TBI + IFNα	98 (81) versus 99 (37)	3.3 versus 1.4	NR (83% 3-year OS) versus NR (77% 3-year OS)	13% versus N/A	5% versus 0%	5%
Hermine et al. [28]	Phase III, randomised	455	R-CHOP + TBI + ASCT versus R-CHOP/R-DHAP + HD-AraC + ASCT	98 (63) versus 99 (61)	3.8 versus 7.3	6.8 versus NR	N/A	4%	N/A
Eskelund et al. [55]	Phase II	160	R-Maxi-CHOP + HD-AraC + ASCT	96 (54)	7.4	NR (64% 10-year OS)	9%	5%	4%
Delarue et al. [56]	Phase II	60	R-CHOP/R-DHAP + HD-AraC + ASCT	100 (96)	6.9	NR (75% 5-year OS)	18%	1.5%	18%
Le Gouill et al. [27]	Phase III, randomised	299	R-DHAP + ASCT versus R-DHAP + ASCT + R maintenance	83 (77)	NR (73% 3-year PFS) versus NR (89% 3-year PFS)	NR (84% 3-year OS) versus NR (93% 3-year OS)	N/A	N/A	N/A
Non-ASCT-based regimens									
Romaguera et al. [31]	Phase II, monocentric	97	R-hyper-CVAD	N/A	4.6	NR (64% 10-year OS)	29%	8%	5%
Merli et al. [32]	Phase II, multicentric	60	R-hyper-CVAD	83 (72)	NR (73% 5-year PFS)	NR (61% 5-year OS)	63%	6.5%	1.5%
Bernstein et al. [33]	Phase II, multicentric	49	R-hyper-CVAD	86 (55)	4.8	6.8	39%	2%	4%

ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP, dexamethasone, cytarabine and cisplatin; CR, complete response; HD-AraC, high dose cytarabine; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; IFNα, interferon alpha; Maxi-CHOP, maximum-strength CHOP; MCL, mantle cell lymphoma; N/A, not applicable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; TBI, total body irradiation; TRM, transplant-related mortality.

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Table 6. Published clinical studies investigating molecular targeted approaches in relapsed MCL

Author	Study features	Assessable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	Median OS (months)
Proteasome inhibitors						
Goy et al. [45]	Phase II	141	Bortezomib	33 (8)	6.7 (TTP)	23.5
mTOR inhibitors						
Hess et al. [42]	Phase III, randomised	54	Temsirolimus 175 mg/75 mg	22 (2)	4.8	12.8
		54	Temsirolimus 175 mg/25 mg	6 (0)	3.4	10.0
		53	Investigator's choice	2 (2)	1.9	9.7
Ansell et al. [43]	Phase II	69	Temsirolimus, rituximab	59 (19)	9.7	29.5
Hess et al. [44]	Phase II	32	Temsirolimus, BR	87 (8)	18	36.0
Immunomodulatory drugs						
Zinzani et al. [38]	Phase II	57	Lenalidomide	35 (12)	8.8	NR
Goy et al. [39]	Phase II	134	Lenalidomide	28 (8)	4	19.0
Trneny et al. [40]	Phase III	254	Lenalidomide	46 (11)	8,7	27.9
			Investigator's choice	23 (8)	5.2	21.2
Wang et al. [41]	Phase II	44	Lenalidomide, rituximab	57 (36)	11.1	24.3
Antibody-based approaches						
Wang et al. [47]	Phase II	32	^{90}Y-ibritumumab tiuxetan	31 (16)	6 (EFS)	21
Ferrero et al. [48]	Phase II	15+[a]	^{90}Y-ibritumumab tiuxetan	40 (20)	3.7	13.8
BCR signalling inhibitors						
Wang et al. [35]	Phase II	111	Ibrutinib	68 (21)	13.9	NR (1.5-year OS 58%)
Dreyling et al. [36]	Phase III	280	Ibrutinib versus temsirolimus	72 (26)	14.6	NR (68% at 1 year)
Wang et al. [37]	Phase II	50	Ibrutinib, rituximab	88 (44)	NR	NR
Kahl et al. [57]	Phase I	16	Idelalisib	62 (N/A)	3 (DOR)	N/A
BCL2 inhibitors						
Davids et al. [53]	Phase I	32 (8 MCL)	Venetoclax[b]	100 (0)	N/A	N/A

[a]Fifteen patients received the antibody as relapse monotherapy, 30 patients as consolidation after salvage treatment.
[b]Not registered in MCL.
BCL2, B-cell lymphoma 2; BCR, B-cell receptor; BR, bendamustine and rituximab; CR, complete response; DOR, duration of response; EFS, event-free survival; MCL, mantle cell lymphoma; mTOR, mechanistic target of rapamycin; N/A, not applicable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Table 7. Recommended follow-up

Examination	Details	Year 1–2	Year 3–5	Year > 5
History	B symptoms	Every 3 months	Twice annually	Annually
Physical examination	Peripheral lymph nodes, liver, spleen	Every 3 months	Twice annually	Annually
Laboratory work-up	Blood and differential count LDH	Every 3 months	Twice annually	Annually
Imaging	Abdominal ultrasound CT neck, chest, abdomen, pelvis	Optional: every 3–6 months	Optional: every 6–12 months	If progress suspected
Toxicity	TSH if irradiated	Annually		

CT, computed tomography; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

limitations in knowing how to react, especially in MRD-positive patients, its use is advised in clinical trials but not recommended in clinical routine, except for the setting of donor lymphocyte infusion post-allograft.

Personalised medicine

In this disease setting, more research is needed to identify molecular markers, which could translate into a more personalised approach.

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Table 8. Summary of recommendations

Diagnostic procedures include histomorphology by an expert haematopathologist, immunophenotype (CD5+, CD19/20+), Ki-67 staining and mandatory detection of cyclin D1 overexpression or t(11;14)(q13;q32)
Clinical and biological prognosticators (MIPI-c) should be applied in clinical routine to estimate the clinical behaviour
In localised stages: discuss conventional ChT followed by RT (30–36 Gy)
In advanced stages:
- Younger patients: HD-AraC containing regimens plus rituximab followed by ASCT and rituximab maintenance
- Elderly patients: conventional immunochemotherapy (e.g. R-CHOP, VR-CAP, BR, R-BAC) followed by rituximab maintenance.

In relapse:
- Targeted approaches (ibrutinib, lenalidomide) should be considered, temsirolimus and bortezomib should be preferably combined with ChT
- In younger patients, an alloSCT should be discussed
- Consider participation in trials

alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BR, bendamustine and rituximab; ChT, chemotherapy; HD-AraC, high dose cytarabine; MIPI-c, combined mantle cell lymphoma international prognostic index; R-BAC, rituximab, bendamustine and cytarabine; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, rituximab, cyclophosphamide, doxorubicin, and prednisone with bortezomib; RT, radiotherapy.

Table 9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America (58).

The selection of the optimal treatment of any given patient is based mainly on clinical and biological risk factors, symptoms and tumour load (Figure 2). PET and MRD-based tailored treatments are currently being evaluated in studies but are not yet part of routine clinical practice.

New agents, especially other inhibitors targeting the B-cell receptor (BCR) pathway, B-cell lymphoma 2 (BCL2) or cyclin-dependent kinases (CDK), are currently being investigated [53].

Follow-up, long-term implications and survivorship

The following recommendations are based on consensus rather than on evidence (see Table 7):

- History and physical examination, blood counts and routine chemistry every 3 months for 2 years, every 6 months for 3 additional years and, subsequently, once a year [V, D].
- Annual evaluation of thyroid function in patients after irradiation of the neck.
- Optional CT scan (or ultrasound examinations to reduce radiation exposure) every 3–6 months for 2 years and every 6–12 months up to 5 years. However, there is no strong evidence to support a regular radiological follow-up. These recommendations are driven by the concern to minimise radiation exposure and lack of evidence for survival advantage conferred with routine surveillance imaging. PET-CT should not be used for surveillance.
- Some studies suggest that pre-emptive treatment may be efficient. However, MRD screening may be carried out but should not guide therapeutic strategies outside clinical studies.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommended treatment strategies outside of clinical studies is provided in Figure 2, and a summary of recommendations is provided in Table 8. Levels of evidence and grades of recommendation have been applied using the system shown in Table 9. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

MD has reported being a member of the advisory board of Bayer, Celgene, Gilead, Janssen, Mundipharma, Sandoz and Roche, received honoraria from Bayer, Celgene, Gilead, Janssen and Roche and research grants from Celgene, Janssen, Mundipharma, Pfizer and Roche; MJ received research support from Janssen,

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